Familial hypercholesterolemia: is it time to separate monogenic from polygenic familial hypercholesterolemia?

Julia Brandts[a,b,*], *Kanika I. Dharmayat*[a,*], *Kausik K. Ray*[a], *and Antonio J. Vallejo-Vaz*[a]

Purpose of review
This review explores the concepts of monogenic and the so-called polygenic familial hypercholesterolemia and how the identification of familial hypercholesterolemia as a monogenic condition and its separation from polygenic primary hypercholesterolemia may have implications for clinical practice.

Recent findings
Through genetic testing, a mutation in any of the three known autosomal dominant familial hypercholesterolemia-causing genes is found in 60–80% of cases with a clinical diagnosis of definite familial hypercholesterolemia. As individuals with a polygenic basis for their hypercholesterolemia do not follow the same inheritance pattern observed in monogenic familial hypercholesterolemia, the use of family-based cascade screening in individuals with a polygenic origin is not recommend, as only 30% of relatives have an elevated LDL-C compared to the 50% in monogenic families. The presence of a causative monogenic mutation associates the highest cardiovascular risk vs. not having a mutation or having a polygenic background, providing prognostic information independent of LDL-C. It may also help assess intensity of interventions. Treatment adherence also seems to be higher after monogenic confirmation of hypercholesterolemia.

Summary
Knowledge about the genetic status of an individual with clinical familial hypercholesterolemia (monogenic vs. polygenic) can provide a more informed understanding to evaluating risk, managing disease and opportunities for screening strategies.

Keywords
dyslipidaemia, familial hypercholesterolemia, genetics, LDL-cholesterol, polygenic risk score

INTRODUCTION

Familial hypercholesterolemia is among the most common genetic diseases in the general population [1,2]. This genetic disorder affects the metabolism of low-density lipoprotein cholesterol (LDL-C), resulting in an impaired hepatic clearance of cholesterol-loaded LDL particles from blood [3]. The life-long exposure to high LDL-C levels from birth ultimately results in a higher risk of atherosclerotic cardiovascular disease (ASCVD), in particular premature coronary artery disease (CAD), among those with familial hypercholesterolemia compared with non-affected individuals in the general population [1,4]. In fact, approximately 20 and 5% of heart attacks occurring among those aged less than 45 and 60 years, respectively, have been attributed to familial hypercholesterolemia [5,6].

Since the first identification of mutations in the LDL-receptor (LDLR) in the 1970s [3] as the cause of raised LDL-C levels in patients with a clinical phenotype we refer to as familial hypercholesterolemia,

[a]Imperial Centre for Cardiovascular Disease Prevention (ICCP), Department of Primary Care and Public Health, School of Public Health, Imperial College London, London, UK and [b]Department of Medicine I, University Hospital RWTH Aachen, Aachen, Germany

Correspondence to Antonio J. Vallejo-Vaz, MD, PhD, Imperial Centre for Cardiovascular Disease Prevention (ICCP), Department of Primary Care and Public Health, School of Public Health, Imperial College London, Charing Cross Campus, St Dunstan's Road, W6 8RP London, UK.
E-mail: a.vallejo-vaz@imperial.ac.uk

*Julia Brandts and Kanika I. Dharmayat contributed equally to the present work.

Curr Opin Lipidol 2020, 31:111–118
DOI:10.1097/MOL.0000000000000675

KEY POINTS

- Through genetic testing, a mutation in any of the three known autosomal dominant familial hypercholesterolaemia-causing genes (*LDLR, APOB* and *PCSK9*) is found in 60–80% of cases that are categorized with a clinical diagnosis of definite familial hypercholesterolemia.
- By using polygenic LDL-C scores, a number of individuals with a clinical phenotype resembling familial hypercholesterolemia but without causative monogenic mutations are shown to have high LDL-C by inheriting a greater than average number of SNPs in LDL-C raising alleles, and they are frequently referred to as polygenic 'familial hypercholesterolemia'.
- The autosomal dominant genetic pattern of monogenic familial hypercholesterolemia enables family-based cascade screening strategies to identify new individuals with familial hypercholesterolemia, whereas this is not routinely recommended in individuals with a polygenic basis for their hypercholesterolemia as they do not follow the same inheritance pattern observed in monogenic familial hypercholesterolemia.
- The presence of a causative monogenic mutation vs. not having a mutation helps identify individuals with the clinical familial hypercholesterolemia phenotype who have a higher cardiovascular risk and atherosclerotic burden, providing prognostic information independent of LDL-C levels.
- Distinguishing between monogenic and polygenic basis for hypercholesterolemia may affect management strategies in different ways, such as intensity of therapy, response to it, adherence to therapy, reimbursement strategies for lipid-lowering medication or genetic counselling.

considerable additional insight into understanding the genetic mechanisms resulting in higher LDL-C levels among those typically classified as familial hypercholesterolemia is now available. In addition, the development of new genetic testing methods, such as the next-generation sequencing, enables faster sequencing of large regions of the genome. However, despite these advances, a causative mutation affecting any of the known familial hypercholesterolemia-related genes is not always found among those individuals having a familial hypercholesterolemia phenotype (primarily identified in clinic by LDL-C levels and additional clinical criteria). On the contrary, new analytical tools, such as genome-wide association studies (GWAS), have permitted the identification of common genetic variants [single nucleotide polymorphisms (SNPs)] with only modest effects on LDL-C levels individually, but when occurring together in the same individual, can lead to high LDL-C and a similar phenotype to that produced by monogenic familial hypercholesterolemia mutations.

As the phenotype of familial hypercholesterolemia (monogenic) and the so-called polygenic 'familial hypercholesterolemia' can overlap, particularly for less-severe cases of monogenic heterozygous familial hypercholesterolemia, and as guideline recommendations for interventions with lipid-lowering medications are primarily guided by the phenotype, that is LDL-C levels, a debate is ongoing on whether monogenic and polygenic disorders should be considered together. However, the identification of familial hypercholesterolemia as a monogenic condition and its separation from polygenic primary hypercholesterolemia may have important implications for clinical practice, from disease detection and screening strategies, to cardiovascular risk evaluation and management of patients.

MONOGENIC FAMILIAL HYPERCHOLESTEROLEMIA AND POLYGENIC 'FAMILIAL HYPERCHOLESTEROLEMIA'

Familial hypercholesterolemia results from a mutation in the genes encoding either the LDL receptor (LDLR) on the hepatocytes surface (resulting in lower-uptake of LDL-C), apolipoprotein B (APOB) (the main apolipoprotein on the surface of LDL particles, which acts as the primary ligand for binding to the LDLR) or proprotein convertase subtilisin/kexin type 9 (PCSK9) (gain-of-function mutations affecting the process of recycling the internalized LDLR, leading to a decrease in the availability of LDLRs on the cell surface) [2]. Individuals with familial hypercholesterolemia can carry the mutation variant in one (heterozygotes) or both (homozygotes) alleles of the affected gene. The vast majority of individuals with familial hypercholesterolemia are heterozygotic, with an estimated prevalence of 1 in 250–350 individuals in the general population; whereas homozygous familial hypercholesterolemia is a rare condition affecting approximately 1 in 160,000–300,000 individuals [7].

Mutations in the *LDLR, APOB* and *PCSK9* genes account for 90–95%, 5–10% and <1%, respectively, of familial hypercholesterolemia cases overall, though the relative frequencies might slightly vary among different regions of the world [8,9]. Although more than 2900 mutations have been identified in the *LDLR*, only a fraction of them, ~1000, have been classified as disease-causing by the American College of Medical Genetics and Genomics guidelines [10]. Within the *LDLR,* pathogenic and likely pathogenic mutations mostly occur as exonic

substitutions and missense rearrangements [10]. Within the *APOB* gene, a single missense mutation in an exon predominantly occurs among those of European ancestry with a higher prevalence in some European countries [8,10]; whereas other regions of the *APOB* gene have been identified, their level of pathogenicity has not been reliably established as of yet.

Because of the challenges and limitations for applying genetic tests widely in clinics or at a population level (monetary and resource-intensive), individuals with familial hypercholesterolemia are routinely detected in the first instance using clinical diagnostic criteria systems that generally consider a combination of LDL-C levels, clinical findings, and personal and family history of premature ASCVD. These clinical criteria usually provide an estimate of the likelihood that a patient may have familial hypercholesterolemia, from 'no familial hypercholesterolemia'/unlikely, to possible, probable and definite familial hypercholesterolemia [1]. The increased understanding of genetics and advancements in and availability/accessibility of genetic tests has led to a greater utilization of these tests to confirm familial hypercholesterolemia diagnosis after applying clinical diagnostic criteria. This progress can also allow the separation, in a large number of individuals, of the clinical diagnosis of familial hypercholesterolemia based on monogenic causes from those individuals with a clinical familial hypercholesterolemia diagnosis, but in whom a causative monogenic mutation is not identified (i.e. having a phenotype resembling clinical familial hypercholesterolemia based on polygenic disorders) (Fig. 1) [1].

Through genetic testing, a mutation in any of the three known autosomal dominant familial hypercholesterolemia-causing genes is found in 60–80% of cases that are categorized with a clinical diagnosis of definite familial hypercholesterolemia, and in 20–30% among those with possible familial hypercholesterolemia, with the remaining deemed to be genetically negative but phenotypically positive [10,11]. The proportion of mutations identified is, however, variable, likely depending, among other potential factors, on the study design, selection and characteristics of the populations studied, number/type of the mutations searched for, how prevalent the studied mutations (vs. other or unknown mutations) are in the population, or the clinical diagnostic criteria used in first instance [e.g. their sensitivity and specificity to accurately capture individuals with (monogenic) familial hypercholesterolemia (pretest likelihood)]. For instance, two studies reported that the prevalence of identified monogenic mutations could be as low as less than 5% among unselected populations with hypercholesterolaemia above 190 mg/dl (i.e. clinical diagnosis based on a single LDL-C cut-off) [12,13], vs., higher percentages reported by other studies frequently using a combination of criteria, such as clinical history, examination findings and LDL-C levels, though still varying widely from approx. 25% to over 85% [10,11,14–16].

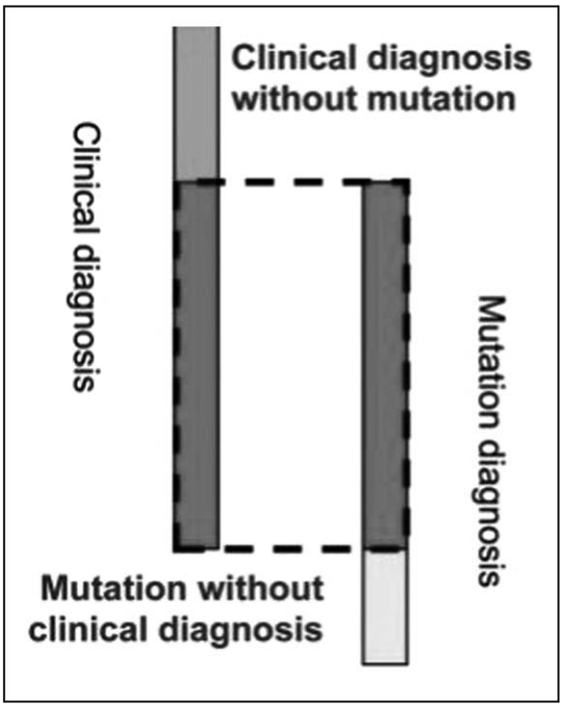

FIGURE 1. Correspondence between clinical (phenotypic) diagnosis and mutation (genetic) diagnosis in patients with heterozygous familial hypercholesterolaemia. Previously published at [1].

In individuals with a clinical diagnosis where a causative mutation cannot be found, the genetic cause is frequently attributed to a polygenic background. Detection of pathogenic mutations by genetic tests is, however, dependent upon various factors, including its yield and technical limitations (e.g. inaccessibility during sequencing to intronic variants and mutations as-yet-undiscovered). Additionally, genetic databases are usually derived from Western populations, which may not be fully applicable to other populations where prevalence/pattern of mutations may vary. As genetic tests become cheaper and more accessible, utilization of these tests is becoming more ubiquitous in regions across the world, though the use of genetic testing, particularly outside Western countries, is still low [17]. Thus, while a polygenic background could explain the familial hypercholesterolemia clinical phenotype in cases where a specific mutation is not found, it cannot be ruled out that in some cases the phenotype may be due to as of yet an unknown monogenic variant.

Polygenic LDL scores

GWAS studies have identified certain genetic variants (SNPs) that are relatively common among the population and that modestly affect plasma LDL-C levels. These SNPs of LDL-C raising alleles are used to derive gene scores [polygenic LDL scores (PGS)], where a compilation of common SNPs are weighted by their impact on LDL-C levels to predict genetically determined hypercholesterolemia besides monogenic causes. By using these scores, a number of cases with a clinical phenotype resembling familial hypercholesterolemia but without causative monogenic mutations are shown to have high LDL-C by inheriting a greater than average number of SNPs in these alleles, and they are frequently referred to as polygenic 'familial hypercholesterolemia'. Although there may be families where there are several individuals whose elevated cholesterol has a polygenic basis, the mode of inheritance is different from monogenic familial hypercholesterolemia, which has an autosomal dominant inheritance.

The proportion of individuals identified depends upon: the SNPs included in the score and; as the PGS is a continuous variable, on the cut-off values (based on an arbitrarily chosen percentile of the general population). For instance, the upper 25th and even upper 10th percentile have been chosen to claim a high PGS. Talmud *et al.* [15] investigated the relationship of LDL-C and a 12-SNP PGS in five European cohorts. They showed a positive association of PGS values (ordinal) with rising LDL-C levels across healthy individuals. Those in the 10th decile of PGS had a 4.17 (95% CI 3.01–5.78) higher risk ratio of having LDL-C more than 4.9 mmol/l than individuals in the first decile. Furthermore, they found mean PGS values to be significantly higher in individuals with phenotypical familial hypercholesterolemia than in healthy individuals [15].

PGSs also have limitations, with similarities to the tests used to identify monogenic mutations. For instance, the discrepancies between clinical phenotype and polygenic test results may be partly explained by the limitations of PGSs. Firstly, depending on the PGS used, different SNPs are considered, which may limit their application to other populations than in those the PGS was derived from. In fact, the strength of the observed association of PGSs and the chosen outcome differ between races [18]. PGSs are based on GWAS that are mainly derived from European-descent populations leading to uncertain accuracy in individuals of non-European ancestry [19▪]. Recent analysis from the UK Biobank showed that the association of a 223-SNP PGS with LDL-C levels was significantly stronger in people of European ancestry than in individuals of African or East Asian ancestry [20▪▪]. Additionally, only the most common SNPs are usually screened; therefore, less common genetic variants (but which could also have a significant effect on LDL-C levels for any individuals carrying them), and also potentially unknown variants having a large effect-size, could be missed by this approach [18]. Lastly, environmental factors and epigenetic regulatory mechanisms influence penetrance of the genetic variants on the expressed phenotype [21]. Thus, individual presentation of exposures based on genetic traits should also be considered. Although this may appear to limit the potential of PGS as a diagnostic dichotomous tool (yes/no, rule-in/rule-out) and may complicate the distinction between polygenic and unknown basis for severe hypercholesterolemia, it nevertheless reinforces the point that in medicine, clinicians should look at all available data, consider strengths and limitations when interpreting diagnostic tests.

Implications for screening

As familial hypercholesterolemia has an autosomal dominant inheritance pattern, upon identification of an individual with familial hypercholesterolemia (index case), the relatives of this individual can be traced either clinically or genetically (if available) to determine if they have familial hypercholesterolemia. Considering the commonality of familial hypercholesterolemia within the general population and that it remains largely underdiagnosed [22], the genetic pattern of monogenic familial hypercholesterolemia is a key to the development and advocacy of screening strategies to identify new individuals with familial hypercholesterolemia and implement measures to prevent ASCVD. In fact, family-based cascade screening (CScr) of index cases has been deemed a cost-effective strategy to identify new cases. Additionally, universal screening (UScr) combined with CScr has been suggested to improve identification at a population level [23,24]. For UScr, given the complexity and limitations around instituting a genotypic screening strategy universally, a first screening step must be applied using a predefined population-based cholesterol threshold that is sensitive and specific to population groups. It has been suggested that, ideally, UScr should be performed by 5 years of age, as screening children enables a more distinct discrimination based on LDL-C allowing delineation between those with (monogenic) and without a pathogenic variant [8,25].

As individuals with a polygenic basis for their hypercholesterolemia do not follow the same

inheritance pattern observed in monogenic familial hypercholesterolemia, the use of CScr in individuals with a polygenic origin is not recommended, as only ~30% of relatives have an elevated LDL-C compared to the 50% observed in monogenic families [11]. This is primarily attributed to the expression and aggregation of SNPs not being identical in relatives (unlike in monogenic familial hypercholesterolemia cases) and complicating the traceability of the SNP variants. Therefore, some authors recommend that families of phenotypic-positive but mutation-negative cases with a high PGS should not undergo CScr [15].

Implications for risk evaluation/stratification

Classical risk stratification models are not applicable in patients with familial hypercholesterolemia. Imaging techniques, for example, coronary artery calcium (CAC) score, may bring independent added value for risk prediction of ASCVD in these individuals, but they have low specificity, particularly in young patients (<45 years) with severe familial hypercholesterolemia [25]. In contrast, recent studies have shown that the presence of a causative monogenic mutation vs. not having a mutation helps identify individuals with the clinical familial hypercholesterolemia phenotype who have a higher cardiovascular risk and atherosclerotic burden, providing prognostic information independent of LDL-C. For instance, Khera *et al.* [12] showed that, for any LDL-C level considered, the risk for CAD is two to three-fold higher in familial hypercholesterolemia individuals with a mutation, compared to individuals with similar LDL-C levels but without a mutation (Fig. 2). Another study detected significantly greater carotid intima-media thickness and higher CAC scores in individuals with a monogenic familial hypercholesterolemia causing variant compared to individuals with an elevated 6-SNP PGS [26].

Trinder *et al.* [27▪▪] compared the risk of premature CVD between monogenic familial hypercholesterolemia, polygenic familial hypercholesterolemia (PGS ≥80th percentile) and patients in whom a genetic cause of familial hypercholesterolemia was not identified. The risk in the monogenic group was significantly higher compared to individuals not having a mutation [adjusted (including LDL-C levels) HR: 1.96; 95% CI 1.24–3.12], Fig. 3. Also, individuals in the latter group seem to have a less severe

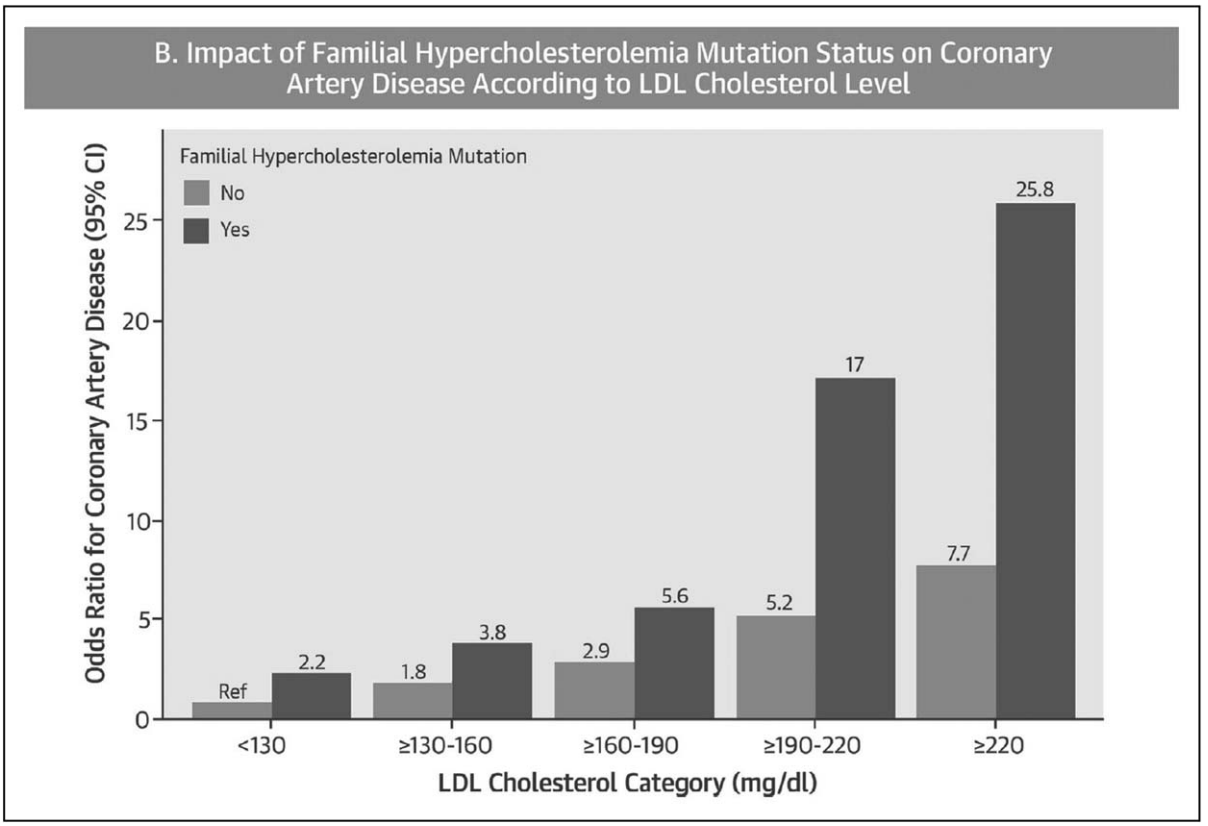

FIGURE 2. Risk of coronary artery disease across different low-density lipoprotein cholesterol levels based on the presence or absence of a familial hypercholesterolaemia mutation. Odds ratios are relative to the category of LDL cholesterol less than 130 mg/dl without a familial hypercholesterolemia mutation. Adjusted for sex, cohort and principal components of ancestry. Previously published at: [12].

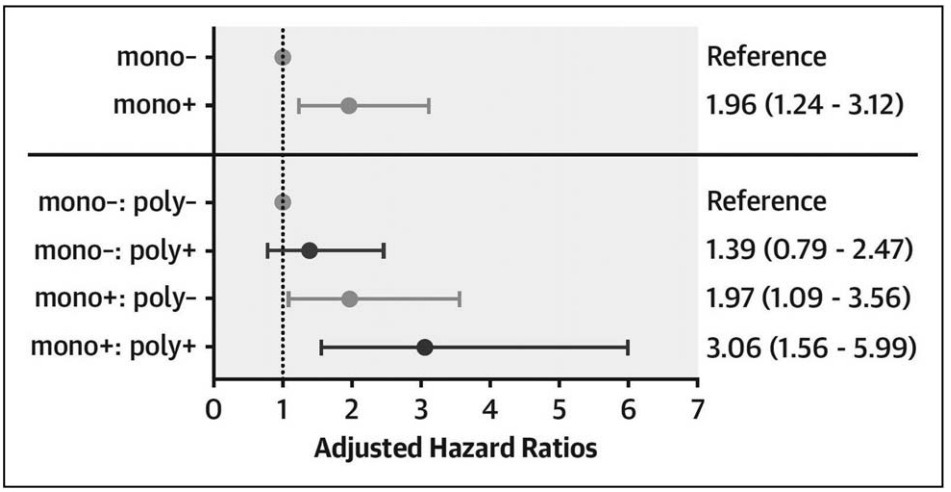

FIGURE 3. Risk of premature cardiovascular disease events based on the monogenetic or polygenic status for familial hypercholesterolaemia. Data are shown as hazard ratios (95% confidence intervals) for premature cardiovascular disease events. Adjusted for age, sex, LDL-C, diabetes mellitus and hypertension. 'mono' refers to monogenic familial hypercholesterolemia; 'poly' refers to polygenic hypercholesterolaemia based on LDL-C polygenic score ≥80th percentile. Previously published at: [27▪▪].

phenotype than those with monogenic familial hypercholesterolemia, with lower points in the Dutch Lipid Clinic Network score and lower LDL-C levels. By comparison, the risk was not significantly different between polygenic hypercholesterolemia and those without a genetic cause identified ($P = 0.30$). Of interest, monogenic familial hypercholesterolemia patients who also had a high PGS had the greatest risk of premature CVD (Fig. 3) [27▪▪]. These results are in line with a more recent study using data on more than 48,700 individuals from the UK Biobank [20▪▪]. Here, individuals with monogenic familial hypercholesterolemia and polygenic hypercholesterolemia (223-SNP PGS >95th percentile) had a higher risk of CVD events compared to those with hypercholesterolemia but without an identified genetic cause, with the monogenic familial hypercholesterolemia group showing the greatest risk (hazard ratio (HR) vs. no genetic cause identified: monogenic familial hypercholesterolemia, 1.93; 95% confidence interval (CI) 1.34–2.77; polygenic hypercholesterolemia, 1.26; 95% CI 1.03–1.55), Fig. 4 [16,20▪▪].

IMPLICATIONS ON MANAGEMENT

As LDL-C is a causal and cumulative risk factor for ASCVD, reducing lifetime LDL-C exposure in individuals with hypercholesterolemia with a genetic background is important irrespective of whether it is monogenic or polygenic, as such individuals are more likely to have a greater duration of exposure. However, distinguishing between monogenic and polygenic basis for hypercholesterolemia may affect management strategies in different ways.

Knowledge about the underlying genetic cause can help decide on the initial treatment intensity. Awareness of a monogenetic cause may imply the need for an early and more aggressive treatment, particularly in the light of the higher risk of ASCVD in this group, as discussed above [12,20▪▪,27▪▪]. It must be also noted, however, that the differences in risk of ASCVD between LDL-C elevations caused by polygenic or monogenic variants may be less marked at older age. For instance, data from the Simon Broome register suggest that the standardized mortality was progressively lower with advancing age among those with monogenic causes [28], therefore, suggesting that irrespective of the genetic basis of elevated LDL-C in older patients, the phenotype, that is elevated LDL-C, should be similarly intensively treated. Knowing the type of mutation may also help assess and anticipate differential responses to lipid-lowering medications [29,30]. For instance, treatment response in terms of LDL-C change from baseline to 1-year after treatment initiation varied between 44% in individuals with LDLR null mutations and 31% for LDLR defective mutations [30]. Additionally, knowing the specific causative mutation in a particular familial hypercholesterolemia individual may open the possibility for the development of future precision medicine individualizing the treatment to each patient/group of patients earlier vs. a watch and wait approach.

Treatment adherence also seems to be higher after monogenic confirmation of the condition [31▪]. Explaining to patients and caregivers about their genetic cause of high cholesterol (not related completely to factors such as unhealthy lifestyle) may help patients and carers accept the need for

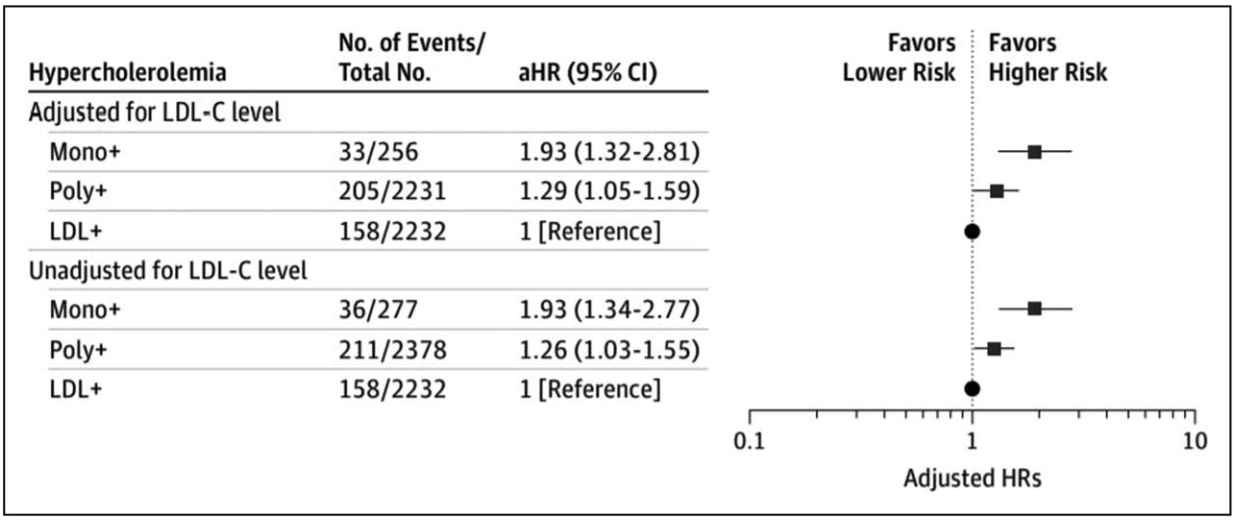

FIGURE 4. Risk of cardiovascular disease events in patients with monogenic familial hypercholesterolaemia, polygenic hypercholesterolaemia and hypercholesterolaemia of unknown genetic cause. Data are shown as hazard ratios (95% confidence intervals) for cardiovascular disease events. Adjustment includes age, sex, genotyping array or batch and principal components of ancestry. 'Mono+' refers to monogenic familial hypercholesterolemia; 'Poly+' refers to polygenic hypercholesterolaemia based on 223 single-nucleotide variants LDL-C polygenic score >95th percentile; 'LDL+' refers to hypercholesterolemia of unknown genetic cause. Previously published at: [20▪▪].

pharmacotherapy earlier and long-term (life-long) therapy and the importance of adherence in order to mitigate risk. Additionally, differentiating between polygenic hypercholesterolemia and monogenic familial hypercholesterolemia may also inform national reimbursement strategies for lipid-lowering therapies. Finally, the identification of a monogenic familial hypercholesterolemia should prompt genetic counselling and discussions about the possibility for the offspring and their potential risk of having familial hypercholesterolemia (whereas this is not that clear with polygenic hypercholesterolemia, where the inheritance pattern is unclear).

CONCLUSION

Knowledge about the genetic status (monogenic vs. polygenic) of an individual with a familial hypercholesterolemia phenotype provides additional information beyond that obtained from LDL-C levels alone and which may have implications for evaluation of risk, disease management strategies and opportunities for cascade screening of relatives.

Acknowledgements

K.K.R. acknowledges the support from the Imperial NIHR Biomedical Research Centre.

Financial support and sponsorship

None.

Conflicts of interest

J.B. and K.I.D. report no conflicts of interest. K.K.R. reports personal fees for consultancy from Abbvie, Amgen, Astra Zeneca, Sanofi, Regeneron MSD, Pfizer, Resverlogix, Akcea, Boehringer Ingelheim, Novo Nordisk, Takeda, Kowa, Algorithm, Cipla, Cerenis, Dr Reddys, Lilly, Zuellig Pharma, Bayer, Daiichi Sankyo, The Medicines Company; Esperion and research grant support from Pfizer, Amgen, Sanofi, Regeneron and MSD. A.J.V.V. reports honoraria for lectures from Amgen, Mylan and Akcea; nonfinancial support from Regeneron Pharmaceuticals, Inc.; and participation in research grants from Amgen, Sanofi, MSD, Pfizer and Daiichi Snakyo to Imperial College London/European Atherosclerosis Society; all outside the submitted work.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Nordestgaard BG, Chapman MJ, Humphries SE, *et al.* Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease – consensus statement of the European Atherosclerosis Society. Eur Heart J 2013; 34:3478–3490.
2. Cuchel M, Bruckert E, Ginsberg HN, *et al.* Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014; 35:2146–2157.
3. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science 1986; 232:34–47.
4. Ference BA, Ginsberg HN, Graham I, *et al.* Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017; 38:2459–2472.

5. Hopkins PN, Toth PP, Ballantyne CM, *et al.* Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011; 5:S9–S17.
6. De Backer G, Besseling J, Chapman J, *et al.* Prevalence and management of familial hypercholesterolaemia in coronary patients: an analysis of EURO-ASPIRE IV, a study of the European Society of Cardiology. Atherosclerosis 2015; 241:169–175.
7. Luirink IK, Braamskamp MJAM, Wiegman A, *et al.* The clinical and molecular diversity of homozygous familial hypercholesterolemia in children: results from the GeneTics of clinical homozygous hypercholesterolemia (GoTCHA) study. J Clin Lipidol 2019; 13:272–278.
8. Sturm AC, Knowles JW, Gidding SS, *et al.* Clinical genetic testing for familial hypercholesterolemia: JACC Scientific Expert Panel. JACC 2018; 72:662–680.
9. Mytilinaiou M, Kyrou I, Khan M, *et al.* Familial hypercholesterolemia: new horizons for diagnosis and effective management. Front Pharmacol 2018; 9:707.
10. Sharifi M, Futema M, Nair D, *et al.* Genetic architecture of familial hypercholesterolaemia. Curr Cardiol Rep 2017; 19:44.
11. Sharifi M, Futema M, Nair D, *et al.* Polygenic hypercholesterolemia and cardiovascular disease risk. Curr Cardiol Rep 2019; 21:43.
12. Khera AV, Won H-H, Peloso GM, *et al.* Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. JACC 2016; 67:2578–2589.
13. Abul-Husn NS, Manickam K, Jones LK, *et al.* Genetic identification of familial hypercholesterolemia within a single US healthcare system. Science 2016; 354:aaf7000.
14. Benn M, Watts GF, Tybjærg-Hansen A, *et al.* Mutations causative of familial hypercholesterolaemia: screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. Eur Heart J 2016; 37:1384–1394.
15. Talmud PJ, Shah S, Whittall R, *et al.* Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. Lancet 2013; 381: 1293–1301.
16. Graham CA, McIlhatton BP, Kirk CW, *et al.* Genetic screening protocol for familial hypercholesterolemia which includes splicing defects gives an improved mutation detection rate. Atherosclerosis 2005; 182:331–340.
17. Vallejo-Vaz AJ, De Marco M, Stevens CAT, *et al.* Overview of the current status of familial hypercholesterolaemia care in over 60 countries: the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Atherosclerosis 2018; 277:234–255.
18. Martin AR, Gignoux CR, Walters RK, *et al.* Human demographic history impacts genetic risk prediction across diverse populations. Am J Hum Genet 2017; 100:635–649.
19. ■ Khera AV, Chaffin M, Zekavat SM, *et al.* Whole-genome sequencing to characterize monogenic and polygenic contributions in patients hospitalized with early-onset myocardial infarction. Circulation 2019; 139: 1593–1602.

This article uses a polygenic risk score for premature myocardial infarction and showed that its prevalence was 11-fold higher among patients with myocardial infarction (age ≤55 years) than a monogenic familial hypercholesterolemia causing variant. Moreover, the study highlights ethnical differences in the application of a polygenic score and presents a statistical approach to adjust for these differences.

20. ■■ Trinder M, Francis GA, Brunham LR. Association of monogenic vs polygenic hypercholesterolemia with risk of atherosclerotic cardiovascular disease. JAMA Cardiol 2020; Epub ahead of print.

This study is the first to show that among the general population, individuals with an elevated PGS for LDL-C have a higher risk of CVD compared to individuals without a genetic basis, despite similar LDL-C levels. Also, the study strengthens the evidence that individuals with a monogenic familial hypercholesterolemia causing variant have the highest risk of CVD compared to individuals with comparable LDL-C levels, but a polygenic or no genetic basis.

21. Guerrero-Bosagna C, Skinner MK. Environmentally induced epigenetic transgenerational inheritance of phenotype and disease. Mol Cell Endocrinol 2012; 354:3–8.
22. Watts GF, Gidding SS, Mata P, *et al.* Familial hypercholesterolaemia: evolving knowledge for designing adaptive models of care. Nat Rev Cardiol 2020; 1–18; Epub ahead of print.
23. Wald DS, Bestwick JP, Morris JK, *et al.* Child–parent familial hypercholesterolemia screening in primary care. N Eng J Med 2016; 375:1628–1637.
24. Futema M, Cooper JA, Charakida M, *et al.* Screening for familial hypercholesterolaemia in childhood: Avon Longitudinal Study of Parents and Children (ALSPAC). Atherosclerosis 2017; 260:47–55.
25. Mach F, Baigent C, Catapano AL, *et al.* 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J 2019; 41:111–188.
26. Sharifi M, Higginson E, Bos S, *et al.* Greater preclinical atherosclerosis in treated monogenic familial hypercholesterolemia vs. polygenic hypercholesterolemia. Atherosclerosis 2017; 263:405–411.
27. ■■ Trinder M, Li X, DeCastro ML, *et al.* Risk of premature atherosclerotic disease in patients with monogenic versus polygenic familial hypercholesterolemia. JACC 2019; 74:512–522.

This article is the first to assess and compare the risk for CV events in a familial hypercholesterolemia phenotype cohort across individuals with monogenic, polygenic or unknown origin. Patients with a monogenic variant showed the highest risk, and no risk differences were found between individuals with polygenic and unidentified genetic origin.

28. Humphries SE, Cooper JA, Capps N, *et al.* Coronary heart disease mortality in severe vs. nonsevere familial hypercholesterolaemia in the Simon Broome Register. Atherosclerosis 2019; 281:207–212.
29. Couture P, Brun LD, Szots F, *et al.* Association of specific LDL receptor gene mutations with differential plasma lipoprotein response to simvastatin in young French Canadians with heterozygous familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 1998; 18:1007–1012.
30. Santos PCJL, Morgan AC, Jannes CE, *et al.* Presence and type of low density lipoprotein receptor (LDLR) mutation influences the lipid profile and response to lipid-lowering therapy in Brazilian patients with heterozygous familial hypercholesterolemia. Atherosclerosis 2014; 233:206–210.
31. ■ Lee S, Akioyamen LE, Aljenedil S, *et al.* Genetic testing for familial hypercholesterolemia: impact on diagnosis, treatment and cardiovascular risk. Eur J Prev Cardiol 2019; 26:1262–1270.

This meta-analysis shows that identification of a genetic diagnosis for familial hypercholesterolemia was associated with improved adherence to treatment and increased rates of statin use. Also, it found variation of CVD risk among different types of LDL-R variants, with a two-fold higher risk in those with LDLR loss of function mutations compared to milder variants.